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Kidney Stones

RUBIN H. FLOCKS

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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Kidney Stones

RUBIN H. FLOCKS

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RENAL CALCULI are composed primarily of a crystalline and organic component. The crystalline portion is interspersed in the organic matrix. The important crystalloids are uric acid, ammoniomagnesium phosphate, calcium oxalate, calcium phosphate and cystine. It is generally agreed that a urinary tract stone requires for its formation a nucleus on which the crystalloids precipitate or crystallize. It would seem that the production of a nucleus should be the same for all types of stones; however, it is possible that the type of nucleus may predispose to a specific crystalloid precipitating on it. In addition, other factors influencing the precipitation of the crystalloid vary with every crystalloid. The type, location, nature and effects produced by the stone vary, depending on where the nucleus is retained and the type of crystalloid precipitating on it.

INCIDENCE

Renal calculi are fairly common. In a 5-year period, 1941-1945, 336 patients with renal stones, out of a total of 100,000 patients, were admitted to the State University of Iowa Hospitals. Approximately one half of all cases of urolithiasis seen during this period had renal calculi. Males were twice as commonly

affected as females. The incidence varies with geography and possibly racial and cultural characteristics. In the United States, the southeastern and southwestern sections are known as "stone belts." Boyce (3) made a study of this factor, found that 7.1 of every 1,000 admissions to general hospitals in the United States are for calculus disease of the urinary tract. The highest incidence was found in the southeastern states and Massachusetts. In three hospitals for Negroes, the incidence was less than 2 per 1,000 in contrast to the 5-12 per 1,000 in other hospitals in the same general region. The incidence of stone as a whole and of each particular type will vary with the predisposing factors which underlie the causes. The varying incidence in race and climate is probably dependent on exposure to vitamin D, volume and character of the urinary output and character of the diet.

FORMATION OF A NUCLEUS

The following factors have been considered of great importance in the formation of a nucleus:

1. Infection.
   (a) Renal parenchyma.
   (b) Urinary passageways.
   (c) Focal infection.
2. Vitamin A deficiency.
3. Toxins.
4. Stasis of urine.
5. Foreign body in the urinary passageway.
6. Formation of a matrix.
7. Changes in the ground substance of the renal pyramid.

Most calculi have, as an important accessory factor or as a major factor in their formation, the presence of infection. Proteus vulgaris, staphylococcus albus, alpha hemolytic streptococcus, bacillus influenzae and bacillus coli have been the main offending organisms. Infection produces a denuded area on the pyramids by direct invasion or from toxins released from a focus of infection on which stone formation may take place. The type of stone will depend on the nature of the infection and the relative solubility of the different crystalloids in the urine when the

nucleus is formed. Clumps of pus cells which become trapped in the calyces may act as a nucleus for stone formation within the urinary passageway. Infection also produces scarring around the infundibula of the calyces, so that poor drainage of the urine from this area results. This predisposes to a stone by trapping crystals of any one of the crystalloids in this poorly draining calyx. These crystals then act as a nucleus for further precipitation of whatever crystalloid happens to be insoluble or by producing stasis and recurrent infections. Any crystalloid may precipitate on the nucleus caused by infection, but if the infection is due to a urea-splitting organism, changes in the solubility of the phosphate are such that the stone will most likely be composed of ammoniomagnesium phosphate.

Vitamin A deficiency as a precursor of urinary calculi in animals has been generally accepted, although its role in this respect in humans is uncertain. Changes occurring within the urinary tract, in cases of vitamin A deficiency, that may contribute to forming the nucleus of a stone are local changes in the epithelium, desquamation of epithelial cells, a change in the pH of the urine toward the alkaline side and precipitation of calcium phosphate or a predisposition to infection.

Retention of urine and precipitated substances is of tremendous importance as an etiologic factor in forming kidney stones. Six per cent of all patients with congenital hydronephrosis due to obstruction at the ureteropelvic junction have stones. "Recumbency" stones are probably formed partly on this basis. Some calyceal stones and stones occurring in calyceal diverticula develop because of obstruction and retention of urine. Retained crystals may act as a nucleus for further precipitation of a crystalloid and the subsequent formation of a stone. Foreign bodies are rarely seen and are of little clinical significance in the formation of renal stone.

Boyce (2) has shown that an organic matrix as a nucleus or template for precipitation of crystalloids may be an important factor in stone formation. He feels that unknown traumatic or toxic factors influence the renal substance to produce or excrete abnormal uromucins. These have the ability to tie up calcium in an insoluble form and act as an organic matrix for precipitation of calcium salts. He supports this theory by separating the

crystalline elements of a stone from its organic matrix by dialysis.

Baker (1) has demonstrated, under conditions of stress and hyperparathyroidism, an alteration of the ground substance of the pyramids, leading to calcification and subsequent stone formation. The importance of this factor and the possibility of it being an intermediate stage in renal infection and hyperparathyroidism in humans is still under study.

PRECIPITATION OF CRYSTALLOIDS

Hyperexcretion of a given crystalloid, changes in the pH of the urine and other changes still little understood may alone, or in combination, cause the precipitation of a crystalloid. In the latter category, changes in the excretion of substances such as citric acid, other salts or protective colloids may be important. It may also be true that various organic matrices act as templates for the crystallization of specific types of crystalloids.

In most instances, cystinuria is a congenital abnormality with recessive inherited characteristics stemming from an inborn error in metabolism. The result is a constant excretion of large amounts of sulfur containing amino acid cystine.

The chemical derangement of this disease is not known, but it has been observed that when the amino acid cystine is ingested by patients suffering with cystinuria, it is oxidized completely to urea and inorganic sulfates. This seems to indicate that the difficulty does not lie in the mechanism which handles the cystine. In fact, there is evidence that the error arises in the metabolic conversion of methionine to cystine.

In addition, there are instances when renal tubular disease may lower the threshold of cystine excretion, with a resultant high urinary cystine. Cystine is particularly insoluble in the pH values of normal urine. However, only 3% of patients with cystinuria form stones. Since cystine is soluble in alkaline urine, the creation of an alkaline urine may prevent this type of stone from forming, despite this metabolic abnormality.

The exact nature of the metabolic abnormality predisposing to excess uric acid excretion is not known. Normally, an adult excretes about 0.7 Gm. of uric acid in the urine, derived from an exogenous source in the diet and an endogenous source from the

metabolism of tissue proteins. Nucleic acids are broken down to purine bases and eventually to uric acid. The rate of excretion of uric acid is directly related to the level within the blood. Therefore, abnormally large amounts in the urine may be the result of (1) an increase in uric acid derived from the ingested nuclear protein or endogenous tissue breakdown, (2) derangement in the fraction of uric acid normally destroyed by oxidation with the production of allantoin or (3) alteration in the renal tubular function, permitting a higher excretion of uric acid.

Uric acid calculi occur 5 times oftener in gouty patients and the high level within the urine is believed to be due to poor reabsorption by the renal tubules. Chronic myeloid leukemia, polycythemia vera and stress through excessive destruction of cells may also produce elevated blood uric acid levels with subsequent high urinary levels.

A low purine diet and maintenance of a urinary pH of 6-7, optimal for uric acid solubility, will often prevent the formation of uric acid concretions within the collecting system of the urinary tract.

Oxalate stones may also be primarily a product of a hyperexcretory state. Oxaluria is not a rare clinical observation. Nothing in the chemistry of urine is known which will significantly alter the solubility of calcium oxalate. Oxaluria apparently results from the coincidental occurrence of a period of hyperexcretion of oxalates with the occurrence of a nucleus or stasis. The exact metabolic derangement associated with oxaluria is unknown, despite extensive work which thus far is difficult to correlate. Increased intake of foods containing oxalate, such as spinach, a special oxalate syndrome and deficiency of magnesium may play a part. It is felt that the presence of other substances such as urea, hippuric acid and citric acid in the urine help to increase the solubility of calcium oxalate and may be important in preventing precipitation in the face of an oxaluria.

The hyperexcretion of calcium and phosphorus plays an important role in the formation of calcium and phosphate stones. In many instances, the etiology of hypercalcinuria may be obscure, and the existing state is referred to as idiopathic hypercalcinuria. However, there are two conditions in which hypercalcinuria is a common finding, namely, in hyperparathyroidism and

in recumbency (Fig. 1). In 83% of hyperfunctioning parathyroid adenomas, renal calculi have developed. Several theories have

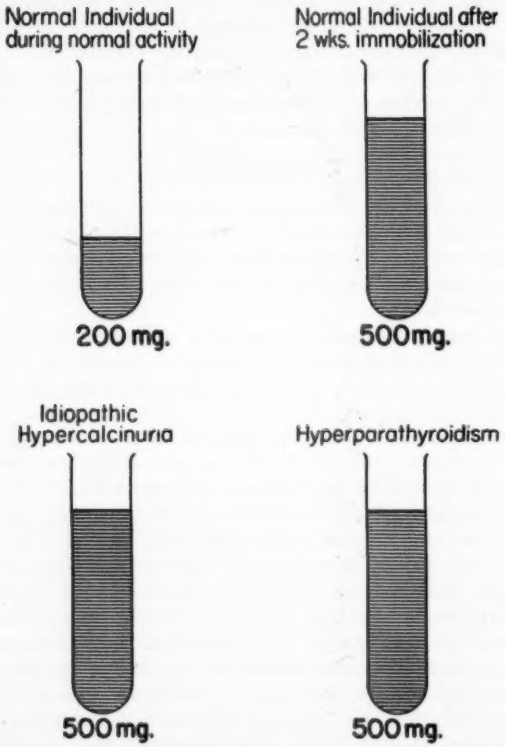

FIG. 1.—Changes in the 24-hour output of calcium in the urine during immobilization. Large amounts of calcium and phosphorus released from the bones result in hypercalcinuria and hyperphosphaturia.

been advanced to explain the action of parathyroid hormone, but the exact mechanism is not definitely established. Its action may be directly on the renal tubules, with a loss of excessive amounts of phosphate in the urine. This loss, in turn, upsets a

constant ratio of serum phosphorus and serum calcium, resulting in the mobilization of calcium and phosphorus from the bones. On the other hand, it may also have an influence on the osteoclasts, which accelerate the tearing down of bone structure and release calcium and phosphorus into the blood stream, with eventual excessive excretion of these elements. Regardless of the mechanism, the end result is a hyperexcretion of calcium and phosphorus.

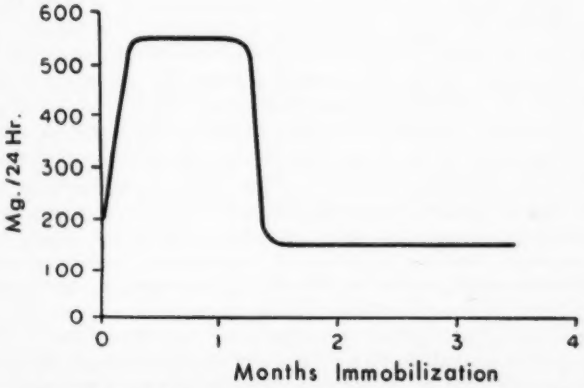

FIG. 2.—Relative 24-hour excretion of calcium and phosphorus during early months of recumbency in renal urolithiasis.

The other condition which leads to excessive excretion of calcium and phosphorus is recumbency. During periods of immobilization, in which the stresses and strains of support normally absorbed by the bones are absent, large amounts of calcium and phosphorus are released from the bones. This phenomenon begins immediately but is usually noted by a hypercalcinuria and hyperphosphaturia between the 1st and 6th weeks of immobilization (Fig. 2). After the 6th week, a new equilibrium of calcium and phosphorus metabolism in the bones is established and the urine values return to normal. During this period hyperexcretion of calcium and phosphorus coupled with stasis of urine in the collecting system and superimposed infection leads to stone formation.

Changes in the pH of the urine are of extreme importance in the pathogenesis of calcium urolithiasis because of the difference in solubility of these crystalloids in acid and alkaline urine. In alkaline urine, the phosphate and carbonates are insoluble. Infection with a urea-splitting organism makes the urine highly alkaline and, therefore, predisposed to the precipitation of such salts. High intake of alkali also may do this, although it is less likely, since less calcium is excreted by the kidney under such conditions.

Besides the factors of pH and quantity per unit of urine, other factors are important in keeping a crystalloid, particularly the calcium phosphate, in solution. Many are unknown and may be of little consequence in some cases. Among the important factors affecting the solubility of insoluble salts is the neutral salt effect. Hammarsten (7) has shown that normal or excessive excretion of magnesium in the urine is helpful in binding the phosphate. That the solubility of the insoluble salts is affected by the amount of colloids present in the urine has not been definitely proved. However, Butt (4) has shown that under certain circumstances the administration of hyaluronidase subcutaneously will increase the protective colloids in the urine. In maintaining the state of supersaturation of the urine until voided, time is important. This explains in part at least the association of stasis with stone formation even when urine is uninfected. It has been emphasized that there are variations in urinary citric acid excretion and the possibility that citrate excretion aids in maintaining calcium in solution by forming a complex ion with it. In addition, Prien has shown that the administration of salicylates will increase the urinary excretion of substances forming complexes with calcium. At present, all these findings are being intensively investigated.

Another important factor with regard to the pathogenesis of renal calculi is the difference in nature and speed of precipitation of the various types of stone. For any type of stone, speed of precipitation depends on the factors producing insolubility of the individual crystalloid. For example, the greater the excess of crystalloid per unit of urine over the amount that may be soluble, the more rapidly precipitation will take place and the faster the stone will grow. Uric acid and calcium oxalate stones grow slowly around their nucleus, whereas cystine and phosphatic

stones grow by rapid accretion and tend to follow the shape of the cavity in which they are forming. Consequently, they are more likely to yield stag-horn calculi. When stasis is present, a stone is likely to grow more rapidly. In addition, infection with a urea-splitting organism will produce calcium phosphate and ammoniomagnesium phosphate precipitation in the stone and add the characteristics of a phosphatic calculus to whatever other characteristics the stone has.

PATHOLOGY OF RENAL STONE

The pathologic picture is a combination of anatomic changes which have made the stone form, the stone itself and the result of its presence. When the calculus is composed of uric acid or calcium oxalate crystals, the nucleus may be on the renal substance or in the urinary passageway either in a calyx, which has previously been scarred, or in the kidney pelvis itself. Usually no infection is present at the time the stone becomes manifest; however, secondary infection may occur following obstruction to the outflow of urine by the calculus. Where the nucleus has been a denuded area on the pyramid, a Randall plaque is formed. The kidney is normal except for the tip of the pyramid. In other cases, the stone is loose in the pelvis or in the calyces. Uric acid and calcium oxalate stones grow slowly, do not follow the contour of the pelvis or calyx and in themselves produce few pathologic changes unless they obstruct the urinary passageways. Varying degrees of pelvic and calyceal dilatation may result from the obstruction. If there is superimposed infection, severe inflammatory reaction in the pelvis and adjacent renal tissues may be present.

In phosphatic stones, many pathologic pictures are possible. The changes may be the same as those outlined for the uric acid and oxalate stones. There may be multiple foci of stone formation which fan into the calyces. This is especially true of the phosphatic stones associated with recumbency. These collections, or "fans," of small stones usually follow the contours of the pyramids but may be present only in the pelvis. When associated with infection, they may "solidify" and form a stag-horn calculus. Given enough time, they grow to form a stag-horn calculus without the

presence of infection. Associated with the formation of a staghorn calculus there is partial obstruction, with dilatation of the pelvis and calyces, atrophy of the renal parenchyma and later inflammatory changes in the renal substance. Unless there is marked hypercalcinuria or marked alkaline infection, precipitations in the pyramids are usually absent on microscopic examination. The formation of early calcium phosphate stones is probably a combination of infection, stasis and hypercalcinuria. The outstanding factor in almost all cases is the presence of small multiple precipitations of calcium phosphate in the calyces and pelvis of the kidney. These precipitations, which form after the onset of predisposing factors, grossly resemble sulfadiazine precipitates. These small stones may pass, or they may fuse to form one or more larger stones; they may act as a nucleus for larger stones or they may be "silent" over a long period. The situation which exists before the stones become intimately mixed with organic material or solidified may be called early calcium urolithiasis. Two points should be emphasized with respect to this phase: first, there may be no clinical manifestations, and second, the peculiar character of the stones requires special therapy to obtain the best results. These early cases of calcium urolithiasis are amenable to irrigation therapy. Usually following removal of these stones, the kidneys are normal and the prognosis is excellent, if the predisposing factors have been corrected. Pathologic changes in cases of simple precipitations around the pyramids or in the kidney pelvis itself consist only of slight irritation of the mucosa by the precipitated particles.

However, with the onset of infection there is much more rapid growth of the stone and more extensive precipitation of crystalloids. In addition, there is round-cell and polymorphonuclear infiltration in the pyramids, precipitation of calcium phosphate in the tubules and ulceration of the tips of the pyramid. Occasionally associated with focal infection there is a localized area of ulceration with plaque formation similar to that described by Randall.

Cystine urolithiasis presents a picture resembling that of calcium phosphate urolithiasis, with three important differences. The stone is relatively non-opaque to x-ray and, therefore, may be missed. For the stone to form and continue to grow, the urine

must be acid. Its rate of growth is slower than that of a phosphatic stone. In addition, with the cystine stone, there is much less likelihood of complicating renal infection.

CHANGES IN KIDNEY AND ADJACENT TISSUE

In early urolithiasis without infection, slight evidence of irritation and ecchymotic areas may occur adjacent to the stones. Sooner or later, depending on the location of the stone, obstruction with subsequent dilatation of the proximal calyces and pelvis supervenes. When obstruction is sudden and complete, atrophy occurs. On the other hand, intermittent obstruction produces hydronephrosis and caliectasis. When infection is superimposed, pyelonephritis develops. In the long-obstructed infected kidney, perirenal fibrosis and induration of the fatty capsule and fat around the pelvis and hilar vessels occur. Extensive scarring around the hilus and the kidney in general makes renal surgery difficult, often necessitating nephrolithotomy instead of pyelolithotomy, or intracapsular nephrectomy when the kidney must be removed. Localized scarring and fatty infiltration may cause poor drainage from a portion of the kidney even after the stone, which was the inciting cause, has been removed. This predisposes to new stone formation. Occasionally the stone may erode through the pelvis, or renal substance or a localized abscess may rupture into the perirenal tissues to form a perinephric abscess; however, this is rather uncommon.

Occasionally extensive, diffuse calcium phosphate concretions form throughout the renal parenchyma, particularly near the tips of the pyramids. This entity has been called nephrocalcinosis. It is not a disease process in itself but a pathologic process. It occurs in the course of other diseases that have changed either the renal substance or the chemical composition of the urine, so that calcium phosphate concretions occur in the parenchyma. Hyperparathyroidism, hyperchloremic acidosis and chronic pyelonephritis have been the primary diseases in most cases. The calcific deposits within the renal substance in hyperparathyroidism result from an increased concentration of calcium in the urine which has resulted from the action of the parathyroid hormone either on the renal tubular cells or the metabolism of cal-

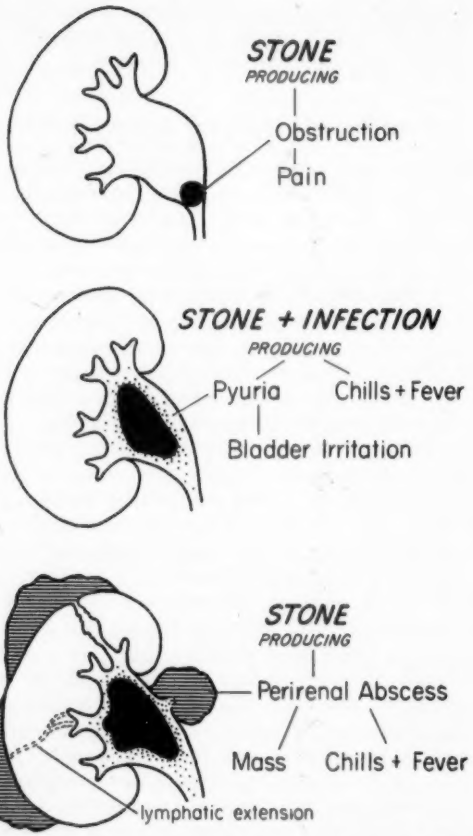

FIG. 3.—Symptoms of renal stone showing conditions of obstruction, infection and abscess.

cium and phosphorus within the bones. Recent studies conducted by Baker (1) have revealed that there is also a change in the character of the intracellular cement substance which encourages the laying down of calcareous material.

Albright has described a state in which renal tubular disease leads to acidosis, with increased mobilization of calcium that occasionally produces nephrocalcinosis. It is thought that a deficiency of carbonic anhydrase in the distal convoluted tubular cells results in a deficient acidification of the urine. Precipitation of calcium phosphate crystals is encouraged by the increased calcium output and the inability of the distal convoluted tubule to excrete acid urine. In addition, there is an impairment of ammonia synthesis, leading to an alkaline urine with an excess of calcium. Under these conditions, calcium phosphate crystals are precipitated diffusely within the renal parenchyma. Fanconi's syndrome also has been associated with diffuse parenchymal calcification. The underlying defect in this disease is thought to be a diminished activity of the enzyme, phosphatase, in the renal tubules. As a result of this abnormality, there is an increased excretion of phosphates, glucose and amino acid. Despite increased ammonia production, the renal mechanism is unable to combat the acidosis, and consequently large amounts of fixed base, including calcium, are excreted in the urine. Because of the hypercalcinuria, diffuse deposits of calcium phosphate may form within the parenchyma.

Recurrent chronic pyelonephritis predisposes to nephrocalcinosis by creating diffuse areas of parenchymal destruction bathed in urine. When renal damage is such that acidosis and hypercalcinuria are superimposed, this results in deposition of calcium salts within the renal parenchyma.

SYMPTOMATOLOGY OF RENAL STONE

The symptomatology of renal stone is based fundamentally on the fact that the stone may produce obstruction or irritation in a portion of the urine passageway. When it obstructs, it causes pain and predisposes to infection (Fig. 3). If it is bilateral, it may produce renal insufficiency. Therefore, the symptoms due to obstruction may be pain, pain with evidence of infection or

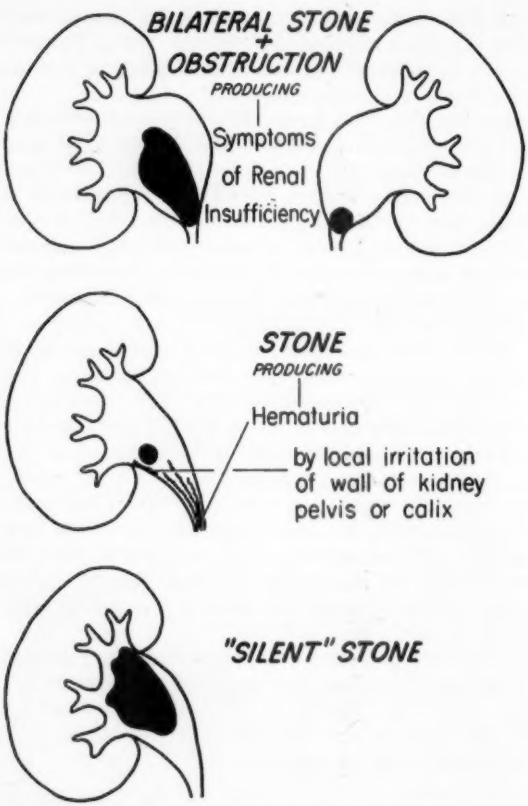

FIG. 4.—Symptoms of renal stone showing conditions producing renal insufficiency and hematuria. Note position of the "silent" type, with no symptoms for a time.

indications of renal insufficiency (Fig. 4). The pain may be referred to other parts of the body, so that the kidney may not be suspected as the site of disease. In addition, the irritation produced by the stone as it moves around the kidney pelvis may produce hematuria, even though obstruction is not present (Fig. 4). The symptoms of kidney stone, therefore, are hematuria, costovertebral angle pain, renal colic, nausea, vomiting, chills and fever; however, for a time a stone may produce no symptoms (Table 1).

TABLE 1.—Presenting Symptoms in 282 Patients with Renal Stone

Renal colic	131
Aching in right flank of abdomen	108
Hematuria	101
Pyuria	49
Chills and fever	87
Bladder irritation	77
Passage of stone	67
Nausea and vomiting	74
Weight loss, weakness, fatigue	21
No symptoms at all	13
Anuria	6
Uremia	4
Mass in region of kidney	9
Symptom of vesical neck obstruction	14
Upper-tract fistula	6

Although a uric acid stone may produce no symptoms for a long time, there is usually little danger to the kidneys, since uric acid stones grow slowly. Usually it moves about, causing pain, hematuria or obstruction before it grows large and produces severe renal damage. It is a non-opaque stone, recognized as a filling defect in the pyelogram or by the fact that it produces obstruction and disturbs the function of the kidney on the pyelogram.

The situation with regard to oxalate stones is essentially the same as that with uric acid stones, differing only in x-ray findings. The oxalate type of calculus is opaque to x-ray.

The outstanding fact with respect to the early symptomatology of calcium phosphate renal lithiasis is that there are no symptoms. Precipitation of the crystalloids and the formation of stone

take place gradually, with varying rapidity, under the influence of the predisposing factors. With no symptomatology, in many cases a diagnosis is first made by means of an x-ray film. After varying intervals, symptoms occur in one or more ways: irritation by small stones, hematuria or ureteral colic. Infection may occur as a result of obstruction caused by the stone. As the result of this, there may be pyuria or generalized symptoms of infection such as chills, fever, leukocytosis and pain over one or both renal regions.

In contrast to uric acid and oxalate stones, cystine and phosphatic stones grow rapidly. A prolonged period of growth of

TABLE 2.—Relative Incidence of Symptoms Associated with Different Types of Stone

Symptom	Uric Acid	Oxalate	Phosphatic	Cystine
Hematuria	++	++	++	++
Pain	++++	++++	++	++
Renal obstruction	++++	++++	+++	+++
Renal infection			++++	+
Renal insufficiency			++	++
Almost no symptoms			+++	++

these stones without symptoms may be associated with extensive renal damage and such marked growth of the stone that its removal at a later date becomes difficult. These stones produce the same symptoms as uric acid and oxalate stones except that frequently there is an associated infection, and at times the outstanding symptoms are those of renal infection (Table 2).

DIAGNOSIS OF RENAL STONE

The diagnosis of renal lithiasis involves not only the demonstration of a stone in the renal pelvis but also answers to the following questions: Are there factors present predisposing to the formation of a renal stone? What is the nature of this renal stone? What is its size, location, number and chemical composition? What are the results of the stone? Is there destruction of renal parenchyma? To answer these questions, an orderly method of procedure must be used for all patients in whom renal stone may be suspected. This consists of a thorough study of the pa-

tient's medical history, physical examination, urinalysis, blood tests and x-ray examination of the urinary tract, a study of renal function and a chemical analysis of the stone.

In all patients presenting a history of abdominal pain, evidence of renal or generalized infection, pyuria, hematuria, symptoms of bladder irritation or evidence of renal insufficiency, a stone must be suspected. The general appearance of the patient may or may not be significant. With acute renal colic, the patient may be in a cold sweat, his pulse may be weak, thready and rapid, or he may be bent over in an attempt to ease the abdominal pain. A patient with acute renal colic frequently moves about restlessly in contrast to the usually quiet patient with an acute intra-abdominal condition. If acute infection is superimposed, chills and fever may be present. In long-standing cases, especially in the presence of suppuration or bilateral nephrolithiasis, there may be loss of weight, sallow complexion and evidences of dehydration. When obstruction is present bilaterally, the clinical picture of uremia may supervene with nausea, vomiting, mental clouding, uriniferous odor to the breath and convulsions.

On physical examination the right or left kidney may be found enlarged because of obstruction, perirenal infiltration or suppuration. There may or may not be muscle spasms in the loin or the costovertebral angle due to reflex spasm of the muscles in this area associated with pain and infection in the kidney. On the other hand, neither kidney may be palpable and no evidence of muscle spasm may be present. It is rare that one can palpate the stone itself; however, in a patient with a large stag-horn stone, this is possible at times.

When a large perirenal abscess is present, findings are typical. Perinephric suppuration in the presence of renal stone is usually due to an extension of the infection from within the kidney. There may be an acute perforation of the pelvis or of the cortex, or the infection may have spread into the perinephric fat by means of the lymphatics. On examination, the abscess usually points posteriorly into the costovertebral angle, producing a fluctuant, hot, sometimes throbbing, area. The abscess usually points in the lower part of the angle between the last rib and the erector spinae muscles in the upper part of Petit's triangle. A high and immobile diaphragm is evidenced on percussion.

The urine is examined for crystalluria, pyuria, hematuria, bacilluria, pH, the quantity of calcium and phosphorus or other crystalloids and the precipitability of the offending crystalloid. Finding crystals in the urine is valuable at times in the differential diagnosis with regard to the chemical nature of the stones. White and red blood cells may or may not be present in the urine. In the presence of aseptic calculus, there is usually a small amount of microscopic hematuria. At times, the kidney with the stone may be completely blocked, so that the urine obtained from

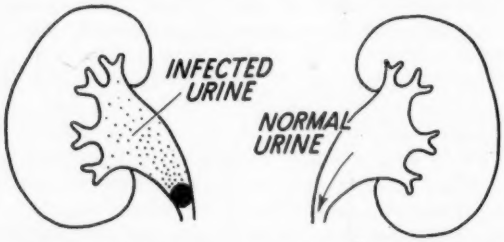

FIG. 5.—Diagnosis of renal stone via the urine. Where obstruction prevents passage of infected urine, bladder urine is normal. If obstruction is intermittent, patient may have chills and fever although urine is normal and, conversely, may be well when it is loaded with pus.

the bladder is that from the normal, or uninvolved, kidney, and thus may be entirely negative (Fig. 5). Also, in the presence of an aseptic stone impacted in the calyx, urine may be entirely negative. In the presence of infection, pus is present. Pyuria may be the only positive finding in cases of urolithiasis.

The presence of bacteria in the urine is important in diagnosing the nature of the stone and indicating the prognosis. Gram-negative bacilli or gram-positive cocci in conjunction with an alkaline urine usually indicate the presence of a urea-splitting organism. This means usually that the stone is phosphatic and, unless the infection is cleared up, recurrence of the stone is expected. Presence or absence of infection is important in prognosis, and, when present, infection must be eradicated before or after removal of the stone to avoid recurrence.

The pH of the urine is measured by means of nitrazine paper. If the pH of the urine is on the acid side, the stone is probably

a cystine or uric acid calculus. If it is on the alkaline side, it is probably a phosphatic, carbonate or ammoniomagnesium phosphate stone. On the other hand, if it is in the range of a pH between 6 and 7, it is probably an oxalic acid stone.

One can also obtain information with regard to the presence of a hyperexcretion of calcium and phosphorus in the urine by a quantitative study of the excretion of these elements in the urine. Qualitative clinical tests also are available for each of these crystalloids.

Precipitability tests may be of therapeutic and prognostic value in some patients. The amount of any crystalloid that will precipitate from a specimen of urine and the ease with which it will do so depend on the quantity of the crystalloid present; also on the pH of the urine, the presence of other salts and other factors, the exact nature of which is yet unknown. Therefore, it is at times desirable to obtain directly a rough estimate of the ease with which a specific crystalloid will precipitate from a particular specimen of urine.

In renal lithiasis, examination of the blood is of value for three reasons: first, the systemic effects of stone may be indicated by a marked anemia associated with long-standing infection and dehydration or renal insufficiency; second, leukocytosis associated with renal infection; and third, the chemical constituents of the blood may change or be abnormal as a result of metabolic abnormalities which have caused the lithiasis, such as changes in the blood calcium and phosphorus associated with hyperparathyroidism. An undernourished, chronically ill patient with low plasma proteins in the presence of a normal total serum calcium may indicate a high uncombined calcium and hyperparathyroidism. Therefore, a low serum phosphorus and hyperphosphaturia are extremely important in establishing the diagnosis of hyperparathyroidism.

Radiography is by far the most accurate and important means of diagnosing kidney stone and the changes it has produced. It gives information not only as to the presence or absence of calculus but also reveals the position, shape and number of stones as well as indicating their nature. It furnishes us with the most accurate method for evaluating the effects of stone or stones. It

is the best method for differential diagnosis of conditions that may simulate renal lithiasis.

X-ray examination of the urinary tract for the presence of stone consists of a plain film including the entire urinary tract, an excretory urogram, a plain film with the ureters outlined by opaque ureteral catheters, and retrograde pyelograms.

In the plain film, the outline and character of the bones, the nature of the soft-tissue shadows and the presence or absence of opacities, which may be stone shadows, are of importance. The presence or absence of curvature of the spine is also important. If a perinephric abscess is present on the right side, the spine will show a scoliosis with a concavity toward the right side. It is important to note the presence of osteoporosis or other bone disease which may be visible in the spine or pelvis. Enlargement of the renal outline on either side may be the result of a renal stone. Perirenal abscess or perirenal fatty infiltration due to stone may obliterate the psoas shadow or enlarge or obliterate the renal outline on the affected side. A uric acid stone does not produce a shadow; therefore, it will not be visible on a plain film. A cystine stone may or may not be visible. Oxalate and phosphatic stones are clearly visible on the plain film.

What are the conditions that may produce confusion on the plain film? Artifacts on the film, gallstones, moles in the skin, calcified lymph nodes, pancreatic stones, calcification of a costal cartilage or tips of transverse processes may produce shadows that could be confused with renal stone. Tuberculous involvement of the kidney or calcification in the renal tumors may produce confusion in the differential diagnosis of renal stone when viewed on the plain film. A definite diagnosis of a stone shadow, as differentiated from some of these conditions, can usually be made by means of density, position and shape of the shadow as well as its relation to the pelvis and renal outline.

The absence of function or the disturbance of function, as noted in intravenous urography, and of negative filling defects, as noted in retrograde pyelography, usually suggests a stone. In the presence of negative filling defects, one must consider tumor of the renal pelvis, blood clots or debris in the kidney pelvis. The differential diagnosis must be made by means of the history, persistence of the filling defect, character of the filling defect and

the nature of other findings in the urine, such as crystalluria.

Pyelography is also important in showing the exact location of the stone and the effects of its presence, such as pyonephrosis, caliectasis and calyceal diverticula. It is important in illustrating whether or not there are conditions present in the kidney, such as congenital calyceal diverticulum or congenital hydronephrosis, that may predispose to the formation of new stone. Therefore, pyelography is indispensable in the study of a patient with nephrolithiasis.

In cases of bilateral renal stone or bilateral renal disease, the blood urea or the blood urea nitrogen is a valuable index of renal function. With a solitary kidney it is indispensable. On the other hand, if one kidney is normal, the blood chemistry is usually normal and, therefore, of little value in estimating the amount of renal damage. Moreover, complete temporary obstruction by the stone may indicate poor function by all the chemical tests and yet not necessarily indicate that the kidney will not recover following removal of the obstructing stone. An estimate of function then will be a combination of excretion tests, such as phenolsulfonphthalein and an estimate of the amount of remaining renal cortex, by a study of the renal outline and its relation to the renal pelvis, as outlined by pyelography.

More exact studies of the nature of the crystalloids composing the stone are usually of great value in outlining the medical management and in indicating the prognosis. These can be made by a chemical analysis of all stones removed from or obtained from the patient.

TREATMENT OF UROLITHIASIS

Objectives of treatment in renal urolithiasis include: prevention of manifest stone formation when conditions known to predispose to urolithiasis have occurred or are occurring; prevention of further renal and urinary tract damage; correction of the damaging effects; removal of the stone and prevention of new stones (Table 3). Thus every chemical type of stone must be treated by a particular regimen designed to achieve the most satisfactory results.

TABLE 3.—Summary of Medical Procedures for Management of Patients with Renal Urolithiasis

A. Accurate history with particular emphasis on:
1. History of vitamin A deficiency
2. History of infection anywhere in the body
3. History of infection, trauma or instrumentation of urinary tract
4. History of recumbency
5. History of metabolic abnormalities
6. History of stress
7. History of previous formation of stones

B. Thorough examination of urine with special emphasis on:
1. Infection (pyuria and hematuria)
2. pH (uric acid and cystine stones, etc.)
3. Urinary excretion of calcium and phosphorus in 24 hours
4. Qualitative test for cystine

C. Complete blood studies with reference to metabolic disorders:
1. Concentration of uric acid in blood
2. Concentration of calcium and phosphorus in serum
3. Concentration of total blood proteins; albumin globulin ratio of serum
4. Value for serum alkaline phosphatase
5. Erythrocyte and leukocyte counts; differential leukocyte count

D. Presence or absence of vitamin A deficiency

E. Search for and removal of foci of infection

F. Treatment of urinary infection, if present:
1. Diagnosis and removal of lesions of urinary tract
2. Administration of fluids
3. Administration of antibiotics
4. Chemotherapy

G. Study of urinary tract itself:
1. Plain roentgenogram
2. Pyelography
3. pH of urine
4. Colloids of urine:
   a. Correct stasis
   b. Remove ulcerated areas and foreign bodies
   c. Alter pH of urine to that best suited for type of stone present
   d. Hyaluronidase (?)

H. Study chemical composition of stone to aid in understanding pathogenesis and to aid treatment

I. Alterations in metabolism and their correction:
1. Cystine
2. Uric acid
3. Calcium

Uric acid calculi are the product of a metabolic disease, and therefore the primary factors responsible in the etiology of this

disease are intrinsic and uncorrectable. These stones are the result of improper metabolism of the nucleoprotein purine, sometimes associated with an excessive excretion of uric acid in the urine. Preventive therapy consists primarily of a low-purine diet, forcing of fluids and medication to adjust the pH of the urine at an optimal level. Even though almost all the excreted uric acid is the result of intrinsic metabolism, the diet should consist of a minimum of foods high in nucleoprotein. A large quantity of fluids should be ingested daily, to afford maximal dilution of the uric acid and provide a mechanical washing, or irrigation, of the renal collecting system. In addition, sodium bicarbonate or another alkalinizing salt should be administered to maintain a urine pH of 6-7—optimal for uric acid solubility.

Since uric acid calculi are metabolic in origin, they are frequently bilateral and usually unaccompanied by infection. They grow slowly and produce little renal damage until they attempt to pass through the ureter. Therefore, their predominant clinical picture is that of obstruction. When this occurs, the obstruction is best relieved by ureteral catheterization, ureteral dilatation and manipulation of the stone with special instruments when it has entered the lower third of the ureter. If this is impossible and obstruction persists and if the stone cannot be removed by ureteral manipulation, ureterolithotomy should be done before irreparable renal damage results.

Cystine stones are similar to uric acid stones in that they are the result of improper metabolism of proteins. Normally, the urine contains only small quantities of cystine, but when the metabolic breakdown of this substance is present, large quantities may be found in the urine. Therefore, the preventive measures should consist of a diet low in protein, supplemented by sodium bicarbonate and large quantities of fluids. The effect of these measures is essentially the same as that just described for uric acid stones.

Cystine stones, like uric acid calculi, are often bilateral and unaccompanied by infection, but differ in that they grow fairly rapidly and often attain stag-horn characteristics. Rarely do they block a ureter, because they are too large to pass. The predominant clinical picture, therefore, is that of renal pain and hematuria due to irritation of the renal pelvis. Since this type of

calculus rarely produces ureteral obstruction, the necessity for ureteral catheterization, dilatation and manipulation of the stone is not often indicated. More frequently, operative removal is necessary.

Calcium oxalate stones, when they occur alone, do not usually form large stag-horn stones. The urine is not usually infected and is usually neutral in pH. The stones are radiopaque, with characteristic serrated appearance. Their cause is not completely known. In many instances they will pass spontaneously because of their small size. The preventive treatment consists of forcing fluids, avoiding infection and stasis in the urinary tract, and dietary management. Regarding dietary management, the important work of Hammarsten of Sweden must be emphasized. She showed that the solubility of calcium oxalate is definitely influenced by the presence of the magnesium ion. It has also been indicated that a diet low in oxalates and high in vitamin B complex is important in decreasing available oxalate in cases of oxalate calculi. Diets adequate in calcium, magnesium and vitamins and low in oxalate may be worked out on the basis of this information.

Studies now in progress seem to indicate that nature maintains the calcium salts in solution in urine not only by the neutral salt effect but by the formation of a sort of complex ion, leaving only a portion of the calcium in the free ionized state. It is the latter that is free to form the insoluble oxalate or phosphate salts and precipitate. Thus diets that increase urinary citrate and those containing phytate, which will form definite complexes with calcium, can lower the effective calcium excretion in the urine and also, of course, lower the effective intake of calcium.

The operative management of oxalate calculi is similar to that of uric acid stones, since oxalate stones are small, usually uninfected, and often gain entrance into the ureter. They differ in that they do not occur bilaterally as often.

If stones do not fall into the uric acid, oxalate or cystine group but are definitely of the phosphate group, the situation is different. Although hyperexcretion of the stone-forming crystalloids is not infrequent as a primary cause of these stones, persistent hyperexcretion of calcium is rare. The most important condition in which this occurs is hyperparathyroidism. If hyperparathyroidism is present, it can usually be determined by blood chemistry,

urinary calcium and phosphorus study, and should be corrected before anything is done about the calculi. If the calculi have been formed as a result of other factors, such as hyperexcretion during a period of recumbency, infection and stasis, or from causes as yet not well understood, treatment necessitates attention to details which at present are thought to be connected with the formation of calculi.

The management of diffuse parenchymal concretions (nephrocalcinosis) is aimed at the underlying primary disease. If a diagnosis of hyperparathyroidism can be established by chemical analysis of the blood and urine, the parathyroid adenoma should be surgically removed. In this way, further progression of the renal damage may be halted. Nothing can be done to offset the renal damage already produced by diffuse calcification. When the disease is secondary to renal tubular acidosis, a low-salt diet should be prescribed and the acidosis further combated by alkalinization with a citrate mixture composed of 140 Gm. of citric acid and 98 Gm. of sodium citrate in 1,000 cc. of water. Correction of the acidosis in the presence of a low serum calcium often produces tetany; therefore it is necessary to administer vitamin D (50,000 units of calciferol daily) and calcium gluconate (5 mg. 3 times a day). If the nephrocalcinosis is secondary to chronic pyelonephritis, the infection should be brought under control with chemotherapy, antibiotics and/or surgical drainage.

In dealing with large phosphatic calculi, three types of therapy are used, any one or a combination of which may be appropriate for the individual patient. These are a dietary regimen, irrigation therapy and surgical therapy.

Prerequisite to the use of dietary therapy is the control of infection. Large doses of appropriate antibiotics and chemotherapeutic agents should be used. The acid-ash diets high in vitamin A, diets containing Basaljel® and low phosphorus may be used, depending on the situation.

Lowering the effective intake and absorption of phosphorus, and thus lowering phosphatic excretion in the urine has proved valuable in certain types of calcium phosphate calculi. The use of aluminum hydroxide gels described by Shorr (9), to prevent the absorption of phosphorus from the gastrointestinal tract and consequently to decrease the urinary phosphorus, has been of

value in certain types of bilateral stag-horn phosphatic calculi of the ammoniomagnesium phosphate type associated with a secondary infection. This type of therapy is also indicated in cases in which the stones have the characteristics of early calcium urolithiasis in which infection is absent or can be controlled and in which there are general contraindications to surgical therapy. It is used also as an adjunct to other types of therapy for preventing recurrence of stones.

Irrigation therapy through a ureteral catheter with either a Suby (10) or a similar solution may also be used for patients with early calcium urolithiasis. There is danger, however, of introducing infection. In cases in which the stone is sand-like in character, very good results can be obtained by this method. The most frequent use of irrigation therapy, however, is an adjunct to surgical removal of large coral-form, or multiple, calculi. In cases in which fragments of small stones have been left behind in the renal pelvis or severe infection is present, postoperative intermittent or continuous irrigation of the renal pelvis can be accomplished through a nephrostomy tube. When used in conjunction with intensive anti-infection therapy and a diet to create a urine of low calcium precipitability excellent results are produced. The forcing of fluids by creating a 24-hour urinary output of at least 2,500 cc. is really a form of irrigation treatment that is essential in the medical management of renal lithiasis. By this means, small precipitates are washed out and cannot become nuclei for further stone formation; moreover, the medium surrounding the stone is kept as free as possible of stone-forming crystalloids.

Operation is indicated in the treatment of a patient with large phosphatic calculi, if infection is present and it appears that complete removal of the stone or stones is possible, either by operation alone or by operation in combination with irrigation through a nephrostomy tube. Great multiplicity of calculi or involvement of the renal pyramids, such as nephrocalcinosis, contraindicate surgical therapy. If operative therapy is instituted, it should be directed not only at removal of the stone but also at a correction of stasis in the urinary passageway. This is absolutely necessary to avoid recurrence of calculi.

Also, when an operation for removal of bilateral or unilateral calculi is planned, it is necessary to consider the influence of

renal counterbalance. When one kidney is normal and there is no metabolic condition that might predispose to recurrent stone, it is more satisfactory to do a nephrectomy for a coral calculus than to remove the stone itself. This is based on the fact that the normal kidney has had to assume almost the entire renal function, so that there will be no stimulus for the diseased kidney to receive. It is preferable also, in the case of bilateral renal calculi when conservative procedures are planned and nephrectomy cannot be considered, to operate on the weaker kidney first. If the more normal kidney is operated on first, it may come back practically to normal, but nephrectomy may then be necessary on the other kidney, for the weaker kidney may not continue to function because of the counterbalancing effect.

Surgical removal of renal calculi will vary according to the size and number of stones, the character and presence of infection and degree of renal damage. Ordinarily, uric acid and oxalate calculi are single, but should they be too large to pass, surgical removal as soon as possible is indicated. With cystine calculi, dietary therapy without recourse to surgery is preferable. If obstruction cannot be relieved by this method, then cystine calculi must be removed surgically. Procedures with respect to phosphatic stones have been described previously.

In suitable cases, stones are removed through an incision made in the renal pelvis or in the parenchyma, or both. The lumbar approach either with or without removal of the 12th rib is the approach of choice.

Once the kidney has been exposed, various instruments and technics are used to aid in removing the stone from the collecting system. The use of the Gibson stone extractor or of the Dees coagulum may be valuable in locating and removing multiple small calculi. In the Dees method, the ureter is clamped off just below the ureteropelvic junction and blood is injected to fill the kidney pelvis. Then thrombin is injected quickly into the kidney pelvis, producing rapid coagulation of the blood. A cast of the kidney pelvis which traps most of the stone fragments is thus formed and removed.

Frequently a needle can be used to locate a small fragment of stone through the renal parenchyma. This can then be removed by using the Creevy stone dislodger.

Roentgenograms of the kidney taken in the operating room are of great value in difficult cases. Combined pyelolithotomy and nephrolithotomy is often necessary to remove large stones or a stone impacted in the calyx. In cases where a kidney is destroyed or severely damaged, so that it is of little functional value and an actual or potential menace to health, nephrectomy is indicated, if the contralateral kidney is in good condition. In some cases, it is beneficial to do a heminephrectomy or calycealectomy for the removal of a portion of the kidney that contains many calculi and in which the drainage system is so impaired that stasis, with recurrent calculi, is almost a certainty. Occasionally, in advanced bilateral renal disease, a nephrostomy, with removal of only easily accessible stones, becomes a lifesaving measure. It is important to realize that in some instances of extensive calculi, with widespread perirenal infection and induration, a nephrectomy may be a difficult procedure. Intracapsular nephrectomy and nephrectomy by morcellation may be necessary (Table 4).

TABLE 4.—SUMMARY OF SURGICAL PROCEDURES FOR MANAGEMENT OF PATIENTS WITH RENAL UROLITHIASIS

A. Relief of obstruction:
1. Ureteral catheterization
2. Pyelostomy
3. Nephrostomy

B. Removal of calculus:
1. Manipulation of calculus obstructing ureter
2. Pelviolithotomy
3. Nephrolithotomy
4. Combined pelviolithotomy and nephrolithotomy
5. Ureterolithotomy
6. Irrigation therapy. May be combined with ureteral catheterization or any of the open surgical procedures listed above.
7. Nephrectomy

C. Surgical correction of predisposing pathologic factors and/or resultant renal damage:
1. Pyeloplasty
2. Heminephrectomy
3. Calycealectomy

The entrance of a small renal calculus into the ureter creates different and peculiar problems in managing the patient. Severe, sharp, knife-like pains begin in the costovertebral angle and radi-

ate around the flank into the lower abdomen, genitalia and inner aspect of the thigh. Temporary relief from pain may be obtained by the use of hypodermics of morphine, Dilaudid® or Demerol®. Smooth-muscle relaxants such as atropine, Banthine®, Transentin®, Octin® and Depropanex® alone or in combination with narcotics are of value in relieving the spasms in the ureteral wall and in facilitating the passage of a stone along the ureter.

More permanent relief from renal colic is obtained only when the obstruction and spasm are abated either by ureteral catheterization, manipulation and extraction of the stone or by ureterolithotomy. The course one chooses to follow in managing a patient with a ureteral calculus depends on many factors. In general, these may be divided into three groups: (1) physical characteristics of the stone, (2) effects of the stone on the urinary tract and (3) the general status of the patient.

If the calculus is small and has not produced a progressive hydronephrosis, an expectant course of therapy can be followed without danger of permanent damage to the kidney. The progress of the stone down the ureter and the status of the urinary tract proximal to the stone should be followed at frequent intervals with excretory urograms.

When the calculus becomes impacted and obstructs the flow of urine, expectant therapy must be abandoned for either cystoscopic manipulation or immediate ureteral lithotomy. If the stone is lodged in the upper two thirds of the ureter, or is larger than 2 cm. in diameter, it should not be manipulated cystoscopically. In addition, hydronephrosis, pyonephrosis, periureteritis, impaction and congenital anomalies of the genital organs are contraindications to manipulation of a ureteral calculus.

On the other hand, if the diameter of the stone is less than 2 cm. and if the stone is located in the lower third of the ureter, with little change in the urinary tract above the stone, attempts can be made to extract the calculus by manipulation. However, one must be aware that manipulation can lead to temporary disability, recurrent attacks of renal colic and a severe febrile course without successful extraction of the stone. Eventually ureterolithotomy may be necessary, if the manipulation fails. In addition, trauma to the ureter by manipulation may produce infection, extravasation with severe damage to the ureter, requiring

an open reparative operation or nephrectomy or stricture of the ureter.

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